



NOTES

COMPLEMENT DEFICIENCIES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- **Genetic diseases:** a protein of the 30+ in complement system missing → abnormal inflammatory/immune response-prone individual

SIGNS & SYMPTOMS

- Recurrent bacterial infection (i.e. pneumonia, tonsillitis, otitis), especially encapsulated bacteria
- Rheumatologic/autoimmune disorders
 - Can be systemic lupus erythematosus (SLE)-like (fever, rash, arthritis, glomerulonephritis)

DIAGNOSIS

LAB RESULTS

- Screening based on recurrent infection/autoimmune familial/individual history
 - Genetic screening
 - Total hemolytic complement (THC/CH50) testing < 11% (measures individual serum's ability to lyse sheep red blood cells (RBCs) coated with anti-RBC rabbit antibody → activates serum complement proteins; AH50 alternative pathway evaluation test)

- Complement component serum levels
 - Level ↓ correlates with specific protein deficiency
 - Overactive pathway consumption → protein level ↓ (i.e. decreased C2/C4 ↓ indicates classical pathway overactivation—as in C1 inhibitor deficiency)

TREATMENT

MEDICATIONS

- **Bacterial infection prevention:** vaccination
 - Meningococcal, pneumococcal, *Haemophilus influenzae b* (Hib) vaccines (conjugated vaccines preferred for Hib pneumococcal)
- Bacterial infection-suspicious symptoms → swift antibiotic management

VISIT...

LANZAROTE
Caliente.COM

C1 ESTERASE INHIBITOR DEFICIENCY

osms.it/complement_deficiency

PATHOLOGY & CAUSES

- Autosomal dominant disorder: C1 inhibitor protein missing → clinical **hereditary angioedema** (HAE) syndrome
- C1 esterase inhibitor role: inhibits C1 protein cleavage in complement cascade
 - C1 esterase inhibitor deficiency → overactive C1 cleavage → ↑ classical complement pathway activation → proinflammatory, ↑ immune responsive state → ↑ downstream anaphylatoxin production (C2a, C4a)
- C1 esterase inhibitor also mediates bradykinin production → hereditary angioedema (HAE)
 - C1 esterase inhibitor absence → ↑ **kallikrein**, factor XII → **unchecked bradykinin production** → vasodilation → severe angioedema

SIGNS & SYMPTOMS

Angioedema episodes

- Commonly last 24–72 hours, without urticaria/pruritis
 - **Frequent prodromal symptoms**: fatigue, nausea, gastrointestinal (GI) symptoms, myalgias present
 - Individuals may report stress (physical/mental) as episode triggers

Edematous episodes

- Nondependent areas, non-pitting
 - **Most common locations**: upper respiratory/GI tract skin/mucosal tissue
 - GI bowel edema → nonspecific GI distress symptoms (abdominal pain, colic)
 - Laryngeal edema most feared → closed airway → asphyxiation

DIAGNOSIS

LAB RESULTS

- Low C1 esterase inhibitor, **C4 levels**

OTHER DIAGNOSTICS

History

- Recurrent, self-resolving angioedema episodes with/without colicky, abdominal pain
- No concurrent angiotensin-converting enzyme (ACE) inhibitors/nonsteroidal anti-inflammatory drug (NSAIDs) use
- Positive angioedema family history

Physical examination

- Nondependent (i.e. head/neck), non-pitting edema areas without urticaria/pruritis

TREATMENT

MEDICATIONS

- **Therapies**: purified C1 inhibitor concentrate, kallikrein inhibitor, bradykinin-B2-receptor antagonist
- If above targeted therapy interventions unavailable → fresh frozen plasma
- **Avoid angiotensin-converting-enzyme (ACE) inhibitors**

SURGERY

- Acute episodes → intubation for airway management

C2 DEFICIENCY

osms.it/complement_deficiency

PATHOLOGY & CAUSES

- **Autosomal recessive disorder:** involves C2 protein absence in classical complement cascade
 - Most common complement deficiency disorder
 - Symptoms commonly present in early childhood
- Associated with IgG deficiency

SIGNS & SYMPTOMS

- Individuals sometimes present with SLE-like symptoms
 - Fever, rash, arthritis, glomerulonephritis
- ↑ infection risk from encapsulated bacteria
 - *Streptococcus pneumoniae*, *Haemophilus influenza* type b, *Neisseria meningitidis*

DIAGNOSIS

LAB RESULTS

- Recurrent SLE-like episodes: CH50 testing

OTHER DIAGNOSTICS

- Clinical/family recurrent, bacterial infection history

TREATMENT

MEDICATIONS

- **Bacterial infection vigilance:** prompt antibiotic therapy
- **SLE-like episodes:** corticosteroids, other immunosuppressants

C3 DEFICIENCY

osms.it/complement_deficiency

PATHOLOGY & CAUSES

- **Autosomal recessive disorder:** involving protein C3 (vital protein connecting three complement activation pathways—classical, alternative, lectin—to final, common pathway)
 - Presents with severe infections shortly after birth
 - Rarest complement deficiency disorder
- **Cleavage product:** C3b (major opsonin)
 - Inability to effectively opsonize without C3b → antigen-antibody complex unable to be phagocytosed → excess immune complex formation, deposition
 - type III hypersensitivity reaction
 - Inability to opsonize underlies frequently encountered sinopulmonary diseases (see bacterial infections below)
- Inability to form C5 convertase → deficient membrane attack complex (MAC) formation
 - Inability to complete complement cascade underlies (primarily meningitis-related) septic presentation
- Abnormal C3 protein levels → abnormal three complement pathway activation → abnormal pathway byproduct concentrations (i.e. anaphylatoxins C2a, C4a) → abnormal immune cell response to immune insult → abnormal neutrophil response → abscess formation

SIGNS & SYMPTOMS

- Severe, recurrent encapsulated bacterial infections shortly after birth
 - Particularly *Streptococcus pneumoniae*
- Children who survive severe infections develop problems secondary to immune complex deposition, reaction
 - Especially membranoproliferative glomerulonephritis

DIAGNOSIS**LAB RESULTS**

- Clinical/family history of recurrent, bacterial infections (especially *Streptococcus pneumoniae*) → CH50 testing

TREATMENT**MEDICATIONS**

- *Bacterial infection vigilance*: prompt antibiotic therapy
- *Bacterial infection prophylaxis*: vaccination
 - Pneumococcal vaccination
 - Meningococcal vaccination (for resulting dysfunctional C5–C9 MAC formation)

C5–C9 DEFICIENCY

osms.it/complement_deficiency

PATHOLOGY & CAUSES

- *Autosomal recessive disorder group*: involving any protein (C5–C9) involved in MAC formation (part of final, common complement pathway)
- *MAC-forming inability*: precludes ability to create osmotic gradient for cellular lysis

SIGNS & SYMPTOMS

- Frequent, recurrent bacterial infection
 - *Propensity for Neisseria gonorrhoeae, meningitidis infections* (thin cell walls → especially complement destruction-vulnerable)

DIAGNOSIS**LAB RESULTS**

- Clinical recurrent, bacterial infection history (especially *Neisseria* species) → CH50 testing

TREATMENT**MEDICATIONS**

- *Bacterial infection vigilance*: prompt antibiotic therapy
- *Severe bacterial infection mitigation*: meningococcal vaccination

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

osms.it/pnh

PATHOLOGY & CAUSES

- **Acquired genetic disorder:** hematopoietic stem cells produce cells that lack cell-membrane protein **CD55** (AKA decay-accelerating factor (DAF)) or **CD59** that predispose cells to **complement-mediated lysis**
 - Involved gene (on X chromosome) is **phosphatidylinositol glycan complementation group A (PIGA)**
 - Biologically-male individuals in early 20s (most common)
- **CD59:** anchor protein for glycosylphosphatidylinositol (GPI), a marker of 'self' antigenicity on erythrocytes, leukocytes
 - CD59 deficiency → cells sensitive to complement-mediated lysis → intravascular hemolysis
 - **Nocturnal:** relative hypoventilation during sleep → slightly ↑ serum CO₂ → slightly acidic serum pH → ↑ complement activity → ↑ nighttime hemolysis

COMPLICATIONS

- Potentially fatal venous (Budd–Chiari syndrome), arterial thrombosis
- Aplastic anemia, myelodysplasia, myelofibrosis, acute leukemia evolution

SIGNS & SYMPTOMS

- Episodic crises triggers include infection, dietary iron supplementation, menstruation
- Nocturnal hemoglobinuria (upon waking)
- Lumbar, abdominal, general musculoskeletal pain

- Splenomegaly may present in severe hemolysis setting
- Venous, arterial thrombosis

DIAGNOSIS

LAB RESULTS

- Normochromic, normocytic anemia; pancytopenia; ↑ lactate dehydrogenase (LDH) tests

Sugar water test

- Serum mixed in sucrose (isotonic solution, low ionic strength) → predisposes to complement-mediated lysis → CD55/59-deficient cells hemolyze

Acid hemolysis test (Ham test)

- Alternative complement cascade triggered in acidified serum conditions → CD55/59-deficient cells hemolyze

CD55/59 protein flow cytometry

- Most sensitive, specific test

TREATMENT

MEDICATIONS

- Glucocorticoids (prednisone; typically poor response)
- **Eculizumab:** monoclonal antibody binds C5 cleavage → prevents MAC formation, complement-mediated cell lysis

SURGERY

- Bone marrow transplantation